# E-1899: An Eastern Cooperative Oncology Group Study Comparing Ketoconazole Plus Hydrocortisone with Docetaxel Plus Estramustine for Asymptomatic, Androgen-Independent, Nonmetastatic Prostate Cancer Patients with Rising PSA Levels

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*Many prostate cancer patients with rising prostate-specific antigen (PSA) levels following radical prostatectomy or radiotherapy receive "early" hormonal therapy, despite its uncertain benefit. When these patients ultimately progress to androgen independence, their management remains controversial, with many receiving second-line hormonal therapy. Chemotherapy for the treatment of advanced prostate cancer has a defined palliative benefit; studies to establish its potential impact on survival are ongoing. E-1899 is an intergroup phase III trial comparing second-line hormonal therapy with ketoconazole plus hydrocortisone with docetaxel plus estramustine in patients with androgen-independent prostate cancer with rising PSA levels who have no evidence of metastases.*
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The widespread application of prostate-specific antigen (PSA) measurement in clinical practice has dramatically shifted the prostate cancer curve to the left, with a significant number of patients now being diagnosed with clinically localized disease. With the presumption that earlier diagnosis and initiation of therapy may result in an increased likelihood of cure, substantial numbers of

Table 1
Selected Trials of Second-Line Hormonal Therapy

| Study | Treatment | No. of Patients | 50% PSA Response | |
|---|---|---|---|---|
| | | | Percentage | Duration (mo) |
| Dawson et al.[18] | Megestrol acetate | 149 | 12 | NR |
| Tannock et al.[3] | Prednisone | 81 | 22 | 4.0 |
| Joyce et al.[19] | Bicalutamide (150 mg) | 51 | 14 | 4.0 |
| Sartor et al.[20] | Aminoglutethimide + hydrocortisone + AAWD | 29 | 48* | 4.0 |
| Small et al.[21] | Ketoconazole + hydrocortisone | 128 | 27 | NR |
| Shahidi et al.[22] | DES (3 mg) | 115 | 32 | NR |

*Percentage indicates those with a > 80% PSA response.
AAWD, antiandrogen withdrawal; DES, diethylstilbestrol; NR, not reported.

patients are undergoing curative-intent therapies, including radical prostatectomy and radiotherapy (external beam and/or brachytherapy). Approximately one third of prostate cancer patients with clinically localized disease (who receive radical prostatectomy and/or radiation) develop evidence of biochemical failure during long-term follow-up. Although it is widely recognized that there is no standard of care for the management of patients with biochemical failure following curative-intent local therapies, androgen deprivation therapy is frequently prescribed, especially for patients older than 65 years. The extensive use of "early" hormonal therapy has resulted in a significant change in the clinical manifestation of patients presenting with androgen-independent disease. Historically, patients received primary androgen deprivation therapy when they developed clinical evidence of symptomatic metastases and clinically benefited from therapy for 24 to 36 months, at which time there would frequently be evidence of clinical and/or radiographic disease progression. Today, with frequent PSA level assessment during the course of hormonal therapy, the majority of patients deemed androgen independent are asymptomatic and oftentimes show no radiographic evidence of disease. Because there is essentially no prospective evidence supporting any therapy in this setting, management of these patients is challenging.

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## Management Options for Patients with Androgen-Independent, Biochemically Defined Prostate Cancer

### *Second-Line Hormonal Therapy*

The management of patients with biochemical progression of prostate cancer following development of androgen independence is a combination of art and science, with a heavy emphasis on the art of medicine. Second-line hormonal therapy is the most widely selected intervention for these patients. The three classes of agents most widely used in this setting are antiandrogens, corticosteroids, and non-corticosteroid adrenal steroidogenesis inhibitors (Table 1).

The potential utility of second-line antiandrogens was first proposed by Fowler and colleagues,[1] who reported significant PSA responses (greater than 50% decline) to flutamide in 80% and 54% of patients with localized and metastatic disease, respectively, who had disease progression following primary hormonal therapy. Fossa and colleagues[2] conducted a phase III study of second-line hormonal therapy in 201 men with advanced, androgen-independent prostate cancer. Patients were randomized to receive flutamide, 250 mg tid, or prednisone, 20 mg in divided doses. There was no significant difference in median time to disease progression or overall survival between treatment groups. A biochemical response was seen in 23% of the patients who received flutamide and 21% of those who received prednisone. There was a statistically significant improvement favoring prednisone in quality-of-life measures. Two subsequent phase III trials comparing mitoxantrone plus corticosteroids with corticosteroids alone demonstrated responses to prednisone (10 mg) and hydrocortisone (40 mg) of 12% and 8%, respectively.[3,4]

Ketoconazole, a substituted imidazole, suppresses testicular and adrenal steroidogenesis by inhibiting the

conversion of cholesterol to pregnenolone. Trachtenberg[5] was among the earliest to report on the potential of ketoconazole to produce clinical responses in patients with previously untreated metastatic prostate cancer. Subsequently, a number of investigators reported modest activity of ketoconazole in patients with androgen-independent disease, with objective response rates of 11%–14%.[6,7] Small and colleagues[8] reported on 50 patients with androgen-independent prostate cancer with either PSA and/or measurable disease progression following antiandrogen withdrawal who received ketoconazole, 400 mg tid, plus hydrocortisone, 20 mg in divided doses. Of the 48 evaluable patients, 30 (63%) had a decline in PSA levels of greater than 50%, with a median duration of response of 3.5 months. The therapy was well tolerated; the most common adverse effects were grade 1 and 2 nausea, fatigue, edema, rash, and hepatotoxicity. Millikan and colleagues[9] conducted a randomized phase II trial comparing ketoconazole therapy with ketoconazole plus doxorubicin in 89 patients with androgen-independent prostate cancer. Fourteen (31%) of the 45 patients who received ketoconazole alone responded to the therapy (≥ 80% reduction in PSA level maintained for at least 8 weeks). The median time to progression was 3.3 months. Toxicity was reported as significant, with 20% of patients in the ketoconazole arm discontinuing therapy because of adverse effects.

*Chemotherapy*

Although extensively investigated in the 1970s and 1980s, systemic chemotherapy was widely thought to be an ineffective therapy for advanced prostate cancer because of its significant toxicity and the limited efficacy associated with its administration. A lack of effective agents and a uniquely difficult neoplasm in which to assess response to therapy using conventional techniques contributed to this belief.

Tannock and colleagues,[3] long-time critics of conventional phase II evaluations of chemotherapy in patients with prostate cancer, conducted a series of clinical trials using novel palliative end points, such as improvement in pain and quality of life, to assess response to therapy. A study of prednisone therapy alone was followed by a phase II trial of mitoxantrone (Novantrone®, Serono, Inc., Geneva, Switzerland), a semisynthetic anthracenedione structurally similar to doxorubicin, in combination with prednisone. In the latter study, 9 of 25 evaluable patients achieved a palliative response, with modest toxicity.[10] These results led to a seminal phase III trial comparing mitoxantrone plus prednisone with prednisone alone. One hundred sixty-one patients with symptomatic androgen-independent metastatic prostate cancer were randomized to receive prednisone, 10 mg daily, or mitoxantrone, 12 mg/m$^2$ every three weeks, plus prednisone, 10 mg daily. A palliative benefit, defined as improvement in pain, was observed in 29% of the patients who received mitoxantrone compared with 12% of those who received prednisone alone ($P$ = .01). The duration of the palliative benefit was significantly longer for the patients who received chemotherapy (median, 43 weeks vs 18 weeks; $P$ < .0001). A similar phase III study conducted by the Cancer and Leukemia Group B (CALGB) in 242 patients demonstrated a delay in time to treatment failure and disease progression favoring the chemotherapy arm but failed to demonstrate a difference in overall survival (12.3 months vs 12.6 months for combination therapy and hydrocortisone alone, respectively).[4] Of particular interest is the fact that the objective response rate to the combination arm was only 7% (4% for hydrocortisone alone).

Because of the limited objective responses produced by mitoxantrone, an array of antineoplastics has been evaluated, with emphasis on agents that target the nuclear matrix and microtubular function.

Estramustine (Emcyt®, Pharmacia and Upjohn, Kalamazoo, MI) is a complex of an estradiol phosphate derivative linked to a nor-nitrogen mustard molecule. Estramustine, initially developed as an alkylating agent, gained FDA approval for use in patients with prostate cancer in 1981. However, its activity in prostate cancer is now believed to be unrelated to its hormonal and alkylating effects. Estramustine binds to microtubule-associated proteins in the nuclear matrix and inhibits microtubular function. Its objective response rate, when taken alone, has been reported to be 14%–48%.[11] For many years following its approval, use of estramustine was minimal because it was widely perceived as providing modest efficacy with a difficult side effect profile. Its reemergence as a potentially important agent for the treatment of advanced prostate cancer is based on evidence that adding estramustine to other antineoplastics with antimicrotubular activity results in an improved response rate.

The taxanes have emerged as the most active class of antineoplastics for the treatment of advanced prostate cancer. Although the initial phase II trial of paclitaxel (Taxol®, Bristol-Myers Squibb Company, New York) given as a 24-hour infusion was unimpressive,[12] research in human prostate cancer cell lines provided evidence that prolonged exposure to paclitaxel enhances the antimitotic effects of estramustine. Additional studies in human prostate cancer cell

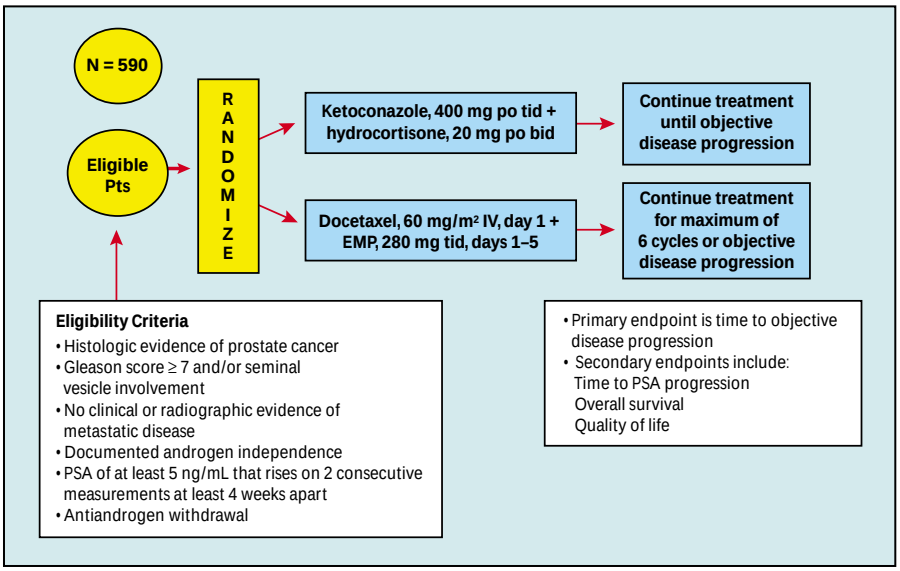


Figure 1. *Schema for E-1899. EMP, estramustine; PSA, prostate-specific antigen.*

lines suggest that chemotherapy resistance in patients with prostate cancer can in part be correlated with bcl-2 overexpression. Haldar and colleagues[13] demonstrated that paclitaxel could induce apoptosis in bcl-2–expressing PC-3 prostate cancer cells via phosphorylation of bcl-2, which may be an effect of taxane-induced cell cycle arrest. Hudes and colleagues[14] subsequently conducted a series of trials of paclitaxel plus estramustine, which demonstrated more interesting levels of antineoplastic activity and led to numerous phase II and subsequent phase III clinical trials evaluating paclitaxel, docetaxel (Taxotere®, Aventis Pharmaceuticals, Bridgewater, NJ), and estramustine.

Docetaxel, a semisynthetic taxoid, has a wide range of activity in several epithelial cancers. In a phase I trial of docetaxel plus estramustine, Petrylak and colleagues[15] demonstrated a 28% objective response rate. Of interest, 7 of the 13 responding patients had previously been treated with estramustine alone. Savarese and colleagues[16] of the CALGB conducted a large phase II trial of docetaxel, 70 mg/m² every three weeks, plus oral estramustine, 280 mg tid for 5 days, plus hydrocortisone, 40 mg daily, in men with advanced prostate cancer. Of the 46 evaluable patients, there was a 50% objective disease response rate, including 3 complete responders. Sixty-eight percent of patients had declines in PSA values of 50% or greater. Combining measurable response and PSA response, the overall response rate was 54%. Neutropenia was common, and 9% of patients had thromboembolic complications. The median length of survival was 20 months.

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## E-1899

### *Objectives, Patient Selection, and Methods*

Patients who have rising PSA levels following hormonal therapy pose a major clinical dilemma—one that is likely to become more common given the aging of the population, the widespread application of prostate cancer screening, and the increased use of curative-intent therapies. The Eastern Cooperative Oncology Group (ECOG) developed E-1899, a randomized trial of ketoconazole (Nizoral®, Janssen Pharmaceutica Products, Titusville, NJ) plus hydrocortisone versus docetaxel plus estramustine, to investigate the effect of second-line hormonal therapy versus systemic chemotherapy on the time to objective disease progression in patients with rising PSA levels following initial hormonal therapy (Figure 1). Secondary objectives include evaluation of time to PSA level progression (attempting to correlate PSA level progression rates with objective progression) and assessment of the impact of both treatments on overall survival and quality of life. An additional secondary objective is to investigate a series of immunohistochemical apoptotic biomarkers as potential prognostic indicators.

Patients eligible for inclusion in E-1899 include those with histologic confirmation of prostate adenocarcinoma with a Gleason score of 7 or higher and/or seminal vesicle involvement at diagnosis. Patients receiving luteinizing hormone-releasing hormone therapy or orchiectomy alone must have PSA levels of at least 5 ng/mL that rises on 2 consecutive measurements at least 4 weeks apart. Patients receiving combined androgen ablation must demonstrate a similar PSA progression following antiandrogen withdrawal (4 week cessation of glucocorticoids or flutamide and nilutamide, 6 weeks for bicalutamide). Patients must have no radiographic or clinical evidence of metastatic disease and must demonstrate castrate

levels of testosterone (≤ 50 ng/dL). Patients who have received systemic chemotherapy within 5 years or have had prior ketoconazole therapy or palliative radiotherapy are ineligible for inclusion in E-1899. Bisphosphonate therapy, if initiated prior to randomization, is permitted.

Patients randomized to the hormonal therapy arm will receive oral ketoconazole, 400 mg tid, plus oral hydrocortisone, 20 bid, until disease progression. Patients randomized to the chemotherapy arm will receive oral estramustine, 280 mg tid (total daily dosage of 840 mg), on days 1 through 5. Following standard steroid premedication, IV docetaxel, 60 mg/m$^2$, will be administered over 1 hour on day 2. Treatment will be repeated every 3 weeks until disease progression or to a maximum of 6 cycles of therapy. Deep venous thrombosis prophylaxis is mandated for patients randomized to the chemotherapy arm. All patients will receive daily an enteric coated aspirin (325 mg) and one of the following therapies: coumadin, 2 mg every other day; enoxaparin sodium (Lovenox®, Aventis Pharmaceuticals, Bridgewater, NJ), 30 mg subcutaneously (sc) every 12 hours; or dalteparin (Fragmin®, Pharmacia and Upjohn, Kalamazoo, MI) 2500 IU sc daily.

*Response Assessment and Statistical Endpoints*

The primary endpoint of E-1899 is time to objective disease progression, which is defined as the development of measurable or evaluable soft tissue disease or bone metastases. A unique aspect of the study design is the intent to keep investigator and patient blinded to PSA level changes during the first 6 months. Change in PSA level is not the primary endpoint of the study. The percentage of patients in each treatment arm with significant declines in PSA levels will be described, as will the kinetics of PSA level declines, including time to nadir and time to rise, constituting progression as defined by consensus criteria.[17] It will be important to correlate clinical outcome (time to first metastasis) with PSA level changes over the course of the study. In an effort to maintain patients in the study until the clinical/radiographic end point is met, PSA levels will be blinded to ensure that each treatment arm receives the therapy prescribed at randomization. PSA levels will be collected throughout the study, batched, and forwarded to a central site for uniform analysis across the study. Because both ketoconazole/hydrocortisone and docetaxel/estramustine are likely to induce decreases in PSA levels, at least initially, the duration of that response in correlation to the clinical end point will be additional useful data obtained from this study.

*The ultimate goal of E-1899 is to determine the appropriate therapy for prostate cancer patients on androgen ablative therapy who have rising PSA levels and no evidence of metastases.*

Despite the study design, it is understood that some patients or treating physicians will have PSA levels obtained separate from participation in the study or determined at the treating facility and shipped to the central site. Treating physicians and patients will be strongly encouraged not to use PSA levels to determine progression, as time to PSA progression is not the primary study end point. If PSA level is used by the patient or the treating physician to define progression, that information will be captured on the case report forms. The study has been powered based on the assumption that nearly 15% of patients/physicians will use PSA level alone to determine disease progression. PSA levels will be made available to the investigator at month 7 at their request. Although these values will be made available, they will not be used to determine disease progression. Patients taken out of the study because of rises in PSA levels will be encouraged to have their scheduled bone scans to determine whether these increases are associated with disease progression.

The ultimate goal of E-1899 is to determine the appropriate therapy for prostate cancer patients on androgen ablative therapy who have rising PSA levels and no evidence of metastases. It is important for both patients and investigators to recognize that there is no compelling information available that indicates whether intermittent and short-lived declines in PSA levels have an effect on survival or time to disease progression. PSA is often used, but is not accepted by the FDA as, an adequate surrogate for important clinical endpoints. This study has the potential to answer the surrogacy question, if patients remain in the study until the primary endpoint is met and are not withdrawn from therapy because of anxiety due to rising PSA levels.

Quality-of-life assessment using the Functional Assessment of Cancer Treatment-Prostate (FACT-P) questionnaire will be administered pretreatment, on day 1 of week 9, at month 6, at 1 year, and annually thereafter.

The primary clinical endpoint is difference across treatment groups in objective progression-free survival at 1 year. With the assumption that 60% of patients will be free of disease progression at 1 year, the enrollment

of 560 eligible patients will allow an 81% power to detect a 35% change in median time to objective progression with an 86% power to detect a 40% improvement in median survival. Interim analyses are planned at time points in which approximately 43% and 79% (36 months and 54 months) of study data will be available.

*Correlative Studies*

The primary objective of PSA laboratory studies is to clarify the usefulness of PSA level as a marker of antitumor response. One objective will be to determine whether there is a difference among treatment arms in PSA velocity during the initial 12 months of the study. The biomarker analysis is designed to evaluate 10 immunohistochemical markers of apoptosis (cIAP2, XIAP, bcl-2, cIAP1, TUCAN, Apaf1, BAG1, p53, MIB1, and cleaved PARP) from radical prostatectomy specimens to test for differences in proportions of high and low expression between patients who experience PSA progression by 1 year and those who do not. In addition, differences in time to PSA progression, objective progression, and survival between high and low expressors of apoptosis will be assessed.

## Conclusion

E-1899 will be an important trial for the treatment of men who have rising PSA levels as the only sign of prostate cancer disease progression after androgen ablation therapy. These men fill our clinics in increasing numbers, and the question of how to treat them surfaces almost daily. The randomization to either of two arms with published PSA response rates of greater than 60% should facilitate the discussion with patients interested in such a study. The SWOG and CALGB will collaborate with ECOG in this high priority study. E-1899 is open through the Cancer Trials Support Unit and has been approved by the Central Institutional Review Board to enhance accrual at sites not directly affiliated with the cooperative groups. Accrual is expected to take place over 2 years. ■

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## Main Points

- The management of prostate cancer patients who are androgen-independent with no radiographic evidence of disease poses a challenge, as there are no prospective data supporting any therapy in this clinical setting.
- Men with biochemical progression of prostate cancer following development of androgen independence are often prescribed second-line hormonal therapy.
- Chemotherapy for the treatment of advanced prostate cancer has a defined palliative benefit; studies to establish its potential impact on survival are ongoing.
- The taxanes have emerged as the most active class of antineoplastics for the treatment of advanced prostate cancer.
- The Eastern Cooperative Oncology Group has developed E-1899, a randomized trial of ketoconazole plus hydrocortisone versus docetaxel plus estramustine, to investigate the effect of second-line hormonal therapy versus systemic chemotherapy on the time to objective disease progression in patients with rising PSA levels following initial hormonal therapy.

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